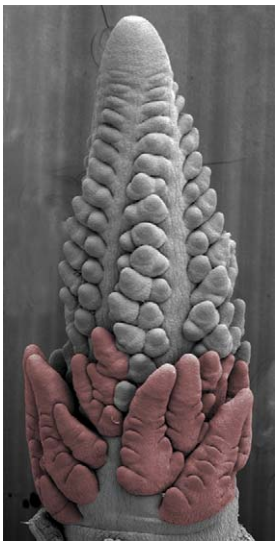
Developmental Biology Select

Cell

Branching is a reoccurring theme in developmental biology. It is observed in individual cells in the case of neuronal axons and dendrites and in the patterning of tissues such as the vasculature of animals or the flowering architecture of plants. This issue's Developmental Biology Select reflects on newly discovered regulators of branching that have been discovered in diverse organisms.



An ear of corn in a *ramosa3* mutant has abnormally long branches at its base. (Image courtesy of N. Satoh-Nagasawa and D. Jackson.)

A Metabolic Enzyme Gives Maize an Earful

Inflorescences are the structures in plants that give rise to flowers. Satoh-Nagasawa et al. (2006) have made the intriguing discovery that a sugar may direct inflorescence branching in maize in a manner similar to that of well-established plant hormones, such as auxin and cytokinin. The authors mapped and sequenced the *RAMOSA3* gene, which when mutated disrupts branching and patterning of seeds in the ears of corn (the female inflorescences). This effort reveals that *RAMOSA3* encodes a phosphatase that converts the sugar trehalose-6-phosphate into trehalose. They find that RAMOSA3 is expressed at the base of the axillary meristem, a structure in the wild-type plant that gives rise to two spikelet meristems each of which subsequently generates two floral meristems. However, in *ramosa3* mutants, the axillary meristem becomes enlarged and the regular pattern of differentiation is disrupted. Satoh-Nagasawa et al. conclude that a trehalose metabolite may be acting as a short-range signal that controls meristem identity. It will be interesting to determine whether trehalose itself is a key signaling molecule that is generated by RAMOSA3 or whether RAMOSA3 acts instead to counteract a signal generated by trehalose-6-phosphate. Moreover, the authors show that *RAMOSA3* acts in parallel with another inflorescence branching mutant *ramosa2* to control the expression level of the transcription factor RAMOSA1. Still to be elucidated is how RAMOSA3 regulates RAMOSA1 expression and which genes are targets of transcriptional regulation by RAMOSA1. A next step will be to understand how the trafficking of these metabolites is regulated to control meristem branching.

N. Satoh-Nagasawa et al. (2006). Nature ***441****, 227–230*.

In Migration, It's Lead, Follow, or Get out of the Way

Migrating epithelial cells communicate with each other to decide who takes the lead and in what order the others will follow, according to Ghabrial and Krasnow (2006). These investigators studied branching in the tracheal network of fruit fly embryos. The tracheal network extends throughout the *Drosophila* embryo and is essential for the delivery of air to internal tissues. During tracheal development, epithelial cells migrate out from an epithelial sac to form a tube, from which secondary and terminal branches are established in subsequent steps. In a screen of genetically mosaic larvae, the authors identified mutant cells that eschewed leadership roles during the formation of dorsal branches of the trachea. This phenotype was shown to result from loss-of-function mutations in Breathless, a receptor tyrosine kinase that binds to the chemoattractant Branchless (a fibroblast growth factor, FGF). The authors confirm that the cells are ordered according to the activity of Breathless, with the cell having the highest activity taking the lead. Yet, as the authors show, being first requires more than just having the most Breathless activity, as the lead cell also actively deters its would-be competitors using Notch signaling. In the absence of inhibitory Notch signaling, most epithelial cells behave like lead cells and cluster at the branch tip, whereas overexpression of Notch disrupts branching altogether. Similar events to those described by Ghabrial and Krasnow may also occur in vertebrates. For example, in the development of the mammalian lung, Fgf10 may behave like Breathless in directing branching morphogenesis. However, it is not yet known whether these epithelial cells communicate with one another to establish an order of migration.

A.S. Ghabrial and M.A. Krasnow (2006). Nature ***441****, 746–749*.

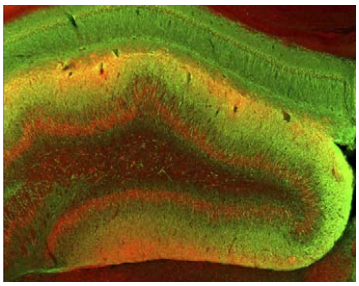
With Synectin's Help, the Arterial Vasculature Is Going Places

Branching morphogenesis is essential to the formation of the vasculature and is governed by the orchestrated migration of endothelial cells. In a tantalizing new study, Chittenden et al. (2006) show that Synectin, a PDZ domain-containing protein that binds to numerous cell-surface receptors, is specifically required for establishment of the arterial, but not the venous, vasculature. The authors studied both mice lacking Synectin and zebrafish embryos in which Synectin expression is decreased. In both cases, a dramatic decrease in arterial branching was observed, whereas the development of the venous system was unaffected. Moreover, arterial endothelial cells from mice lacking Synectin were defective in tube formation and migration in vitro. Close examination of these cells revealed that

activated Rac1, which is required for lamellipodia formation, does not cluster at specific cellular locations to polarize the cell when Synectin is absent. Synectin binds to numerous receptors involved in angiogenesis, including the FGF receptor Syndecan-4 and Neuropilin-1. Although the mechanism by which Synectin acts in endothelial cell migration is not clear, the authors suggest that a critical function may be to transport activated Rac1 to the cell's leading edge. Previous work has shown that integrins may promote Rac1 localization to lamelliopodia by limiting the internalization of lipid rafts that act as Rac1 anchorage points. This work raises the question of how Synectin may be integrated in these dynamic events.
T.W. Chittenden et al. (2006). Dev. Cell ***10****, 783–795*.

Neuronal Dendrites Need An ESCRT

In *shrub* mutants of *Drosophila*, a subset of sensory neurons have dendritic arbors that are decreased in size but are more highly branched. Now, Sweeney et al. (2006) report that *shrub* encodes a coiled-coil protein homologous to a critical component of the yeast ESCRT-III complex that is involved in the transport of proteins via the endosomal pathway to multivesicular bodies. Indeed, in *shrub* mutants, endosomal markers have altered subcellular distributions, suggesting that a change in endosomal trafficking is responsible for the abnormal neuronal morphology. Although it is likely that loss of Shrub would affect the localization, expression, and activity of many neuronal proteins, the authors make the intriguing observation that the processing of Notch, a known regulator of dendritic morphology, is disrupted in *shrub* mutants. Disruption of an endosomal compartment could alter the intensity and duration of signaling by cell-surface receptors, resulting in modulation of branching complexity.
N.T. Sweeney et al. (2006). Curr. Biol. ***16****, 1006–1011*.



Immunostaining for Map2 (green), a marker of neuronal dendrites, and phosphorylated Akt (red) reveals the dramatic hypertrophy in the dentate gyrus of mice lacking Pten in a subset of differentiated brain neurons. (Image courtesy of C.-H. Kwon.)

Pten Mutants Branch out

Pten, a lipid phosphatase, is best known as a tumor suppressor protein that acts upstream of Akt kinase. Kwon et al. (2006) now show that loss of Pten in mature neurons of the mouse stimulates the growth and branching of axons and dendrites and increases the density of dendritic spines (the interface where synapses are located). They show that loss of Pten leads to activation of the Akt/mTOR signaling pathway, which is known to stimulate protein synthesis. Localized protein synthesis in dendrites can regulate synapse activity and may underlie the correlation observed by Kwon and colleagues. Interestingly, the mice with neuronal Pten deficiency studied by Kwon et al. show decreased interest in unfamiliar mice, even though their interest in novel inanimate objects is equivalent to that of wild-type mice. In addition, these mutant mice have a heightened startle response to noise and display anxiety behaviors. Previous work by others has identified mutations in PTEN and the AKT pathway in humans as potentially contributing to multiple brain disorders including autism, which is characterized by impaired social interactions and hypersensitivity to sensory stimuli. Kwon et al.'s mouse model could be used to test potential interventions for disorders associated with excessive dendritic spine density. For example, future work may establish whether treatment of these mutant mice with an mTOR inhibitor, such as rapamycin, could restore normal neuronal morphology and improve their social interactions.
C.-H. Kwon et al. (2006). Neuron ***50****, 377–388*.

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